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Percutaneous Autologous Bone Marrow Transplantation for Nonunion of the Femur

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Abstract

Percutaneous bone marrow injections were performed on 7 nonunions of the femur. There were 6 hypervascular nonunions and one avascular nonunion. Two nonunions presented with active infections. One other patient had a history of infection which had subsided. One nonunion received the injection twice. After the site of nonunion was curetted and the bone surface was scored, 150 ml of bone marrow aspirated from the iliac bone was injected. Complete union occurred in 4 patients within 9 months; all of them were uninfected hypervascular nonunions following intramedullary nail fixation. One nonunion with a bone defect united partially leaving a 1 × 1 cm defect. The two infected femoral nonunions failed to unite. The results show that percutaneous autologous bone marrow injection for femoral nonunions can be considered for uninfected hypervascular nonunions following intramedullary nail fixation. In these cases, stimulation of healing processes of fracture leading to consolidation can be expected from bone marrow injection. However, femoral nonunion with an active infection and loss of fixation is considered to be a contraindication for this technique.

Introduction

It has been proposed that failed or delayed fracture healing can be repaired with the aid of autologous bone marrow transplantation. The marrow contains osteogenic precursor cells which can contribute to bone formation[2,3,6,11,18]. Animal experiments have revealed that bone defects or nonunions can be repaired with the aid of a bone marrow graft[17,19,21]. Since the first report by Connolly et al[7], clinical studies have demonstrated that nonunions are healed by percutaneous autologous bone marrow injections[9,10,12–14,20]. So far, however, strict indications and contraindications for this method have not been established. Furthermore, previous reports are mostly based on experiences with tibial nonunions. It is not clear whether or not percutaneous bone marrow injection into femoral nonunions can yield the same clinical effects as in tibial nonunions. Obviously anatomical and biomechanical environments of the femur are different from those of the tibia.

We present the results of bone marrow injection into femoral nonunions. The role and indica-

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tion of bone marrow injection in the treatment of nonunions are discussed.

Patients and Methods

From 1992 to 1995, autologous bone marrow injections were performed on 7 nonunions after fracture of the femur. In this study, a fracture was judged to be a nonunion if it had not demonstrated radiographic healing and had caused pain and movement for more than 7 months after the initial treatment[9]. The patients consisted of 4 males and 3 females with an average age of 53.4 years and a range of 24 to 70 years. Two nonunions with apparent infection were included in this study. One patient received the injection 2 times into the same site. The amount of time between initial treatment and bone marrow injection ranged from 9 to 34 months, with an average of 17 months. There were 6 mid-shaft fractures and one distal shaft fracture. Nonunions were classified according to the method proposed by WEBER[22]. There were 6 hypervascular nonunions and one avascular nonunion.

At the time of the marrow injection, 6 of 7 nonunions had been fixed by intramedullary nails, and the remaining one which was infected was fixed by Hoffmann type external fixator. Intramedullary nails consisted of Universal nails in 2, Ender pins in 2, Russel-Tailor nail in one, and Huckstep nail in one. Five intramedullary fixations except for the Huckstep nail had been performed closed.

Two patients presented persistent infection at the fracture site. Bacterial examination revealed methicillin-resistant staphylococcus aureus (MRSA) and staphylococcus epidermidis as the causative organisms in both. There were no sinuses. Another patient had a history of infection which had subsided at the time of bone marrow injection. Each of these 3 patients had undergone more than 2 surgical interventions before bone marrow injection. Previous treatments include plate fixation, intramedullary nailing, irrigation, external fixation, conventional iliac bone graft, vascularized bone graft, and electric stimulation (Table 1). The 2 nonunions with apparent infection had lost stable fixation and stress radiographs showed more than 9 degrees of abnormal movement at the nonunion sites. Six of 7 bone marrow injections were performed as the sole procedure, but one patient received intramedullary nail replacement simultaneously. The patient who had previously had an infected nonunion received 2 injections in the same site. In this case, the fracture partially united after the first bone marrow injection, but a bone defect 1×1 cm in size was left unrepaired. The second injection was performed 10 months after the first one. For all the patients, the procedure was per formed in a hospitalized condition. The duration of admission ranged from 3 weeks to 10 months, with an average of 4.6 months. The patients with infected nonunions stayed in the hospital for more than 8 months, whereas the patients with uninfected nonunions stayed for 1.2 months on average. The follow-up period ranged from 15 to 47 months, with an average of 37.8 months. There were no refractures.

Procedure of autologous bone marrow injection

The procedure was performed under general anesthesia in 2 patients with infected nonunions and one patient who underwent nail replacement. For the remaining patients, it was performed under spinal anesthesia. The patient was placed in the lateral position under general anesthesia. Under the control of an image-intensifier, the fibrous tissues at the nonunion site were curetted and the bone surface was scored with a curette percutaneously through a skin incision of about 10 mm. After the wound was closed, bone marrow was aspirated from the posterior iliac wing using aspiration needles (Jamshidi series 11G, Baxter) and 5 or 10 ml syringes. Ten to 15 ml of bone marrow

Table 1 Patients' clinical data.

Case	Age Sex	Weber's Classification	Methods of Fixation *	Previous Ttreatments	Infection	Result
1	70 M	hypervascular	Ender pins	None	Absent	Union
2	52 F	hypervascular	Russel-Taylor nail	None	Absent	Union
3	24 F	hypervascular	Universal nail	None	Absent	Union
4	51 F	hypervascular	Universal nail	None	Absent	Union
5	54 M	hypervascular	Huckstep nail	Intramedullary nail (Zickel nail)	Previously present	Partial Union
6	65 M	hypervascular	Ext. fixator	Plate fix., Bone graft, Vascularized bone graft, Electric stimulation	Present	Failure
7	58 M	avascular	Ender pins	Intramedullary nail, Irrigation, Bone graft	Present	Failure

Nail replacement was performed at the time of bone marrow injection in case 2.
*: Methods of fixation at the time of bone marrow injection.

were taken from each aspiration site. A total volume of 150 ml of marrow was injected into the nonunion site through a 16 or 14 G needle. The number of nucleated type cells in the aspirated marrow was measured in 3 patients.

Management after bone marrow injection

In 5 patients without apparent infection, weight bearing was prohibited for 2 weeks, after which walking using a cane was permitted. Patients' daily activities were not restricted, and they were encouraged to do as they did before the injection. This post-injection management was intended to minimize the effect of fracture immobilization on healing. After pain disappeared, full weight bearing was permitted. In the 2 patients with infected nonunions, non-weight bearing was continued.

Results

Nonunion was judged to be healed when cortical trabecular bridging occurred in radiographs and pain disappeared. The 2 nonunions with persistent infection failed to heal and the one nonunion with a bone defect partially united. The remaining 4 completely united. Healing was achieved radiographically from 5 to 9 months after bone marrow injection. Pain disappeared earlier than radiographic consolidation. In one patient, the nonunion with a bone defect of 1×1 cm in size remained even after the second injection. In this patient, there was temporary elevation of erythro-

cyte sedimentation rate and C reactive protein after both the first and the second injections, but there was no discharge. The nonunions which resulted in complete union or partial union had been fixed by intramedullary nails at the time of bone marrow injection and were all hypervascular nonunions. Measurement of bone marrow cells revealed that the average number of nucleated type cells was $3.6 \times 10^4/mm^3$ (Fig. 1 and Table 2). There were no complications associated with the procedure.

Illustrative cases

Case 1

A 70 year-old man sustained a closed fracture of the right femur. Radiographs showed marked increase in anterior bowing of the femoral shaft. The border between the cortex and the marrow cavity was not clearly distinguished. He had a history of osteomyelitis of the femur during his childhood, which was believed to be the cause of the radiographic abnormality. The fracture was internally stabilized with 5 Ender pins. Subsequently, 3 pins became loosened and spontaneoussly immigrated within 3 months after the operation. Therefore, these 3 pins were eventually removed, and 2 pins remained. Twenty-five months after the operation, the fracture was judged to be a nonunion (Fig. 2). A total volume of 150 ml of bone marrow was injected into the nonunion site. Weight bearing was prohibited for 2 weeks, after which partial weight bearing was permitted. No plaster immobilization was applied. Nine months after bone marrow injection, the fracture was almost united (Fig. 3).

Case 2

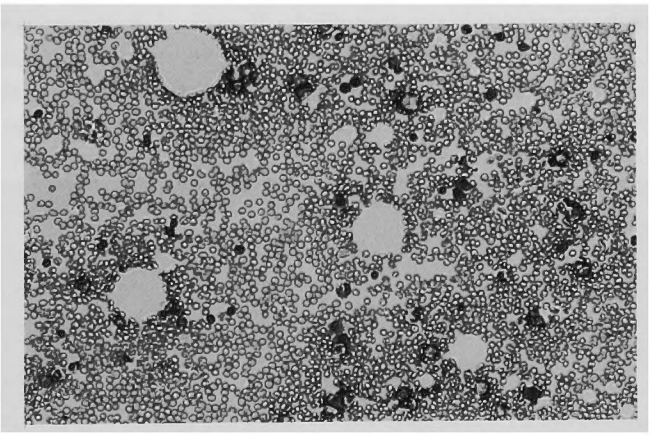

Fig. 1 Photomicrograph of the aspirated bone marrow in Case 5 (× 125).

Table 2 Number of nucleated type cells in the aspirated marrow and clinical results.

Case	Age	Number of Cells	Results
1	70	3.3 (x $10^4/mm^3$)	Union
2	52	2.9	Union
5	51	4.6	Union

Fig. 2 Case 1. Aseptic hypervascular nonunion 2 years after the injury in a 70 year-old man. Radiographs before bone marrow injection. a: A–P view, b: Lateral view

A 65 year-old man sustained a distal shaft fracture of the right femur. The fracture was initially treated with an interlocking intramedullary nail in another hospital. The fracture became infected. In spite of continuous irrigation for 2 weeks followed by conventional bone graft, the fracture did not heal. A Hoffmann type external fixator was applied. In spite of these procedures the fracture did not completely heal. Twelve months after the injury, bone marrow injection was performed. At the time of bone marrow injection, stress radiographs showed about 9 degrees abnormal movement

Fig. 3 Radiographs after bone marrow injection showing the process of healing. Changes in radiographic findings with time after the injection apparently differ from those before the injection. a: 2 weeks, b: 7 weeks, c: 11 weeks, d: 36 weeks

Fig. 4 Case 6. Infected hypervascular nonunion in a 65 year old man 12 months after the injury. Stress radiographs showed about 9 degrees abnormal movement at the nonunion site.

at the fracture site (Fig. 4). The nonunion has not healed 2 years after bone marrow injection.

Discussion

Autologous cancellous bone graft has been the most reliable treatment of nonunions because of its osteoinductive and osteoconductive properties, osteogenic cell introduction and immunological safety. However, it has several disadvantages. Risks for postoperative morbidity at the donor site and for occurrence of infection at the recipient site are major drawbacks[15]. In light of these complications, autologous bone marrow injection into the nonunion site as a substitute for operative bone grafting has become utilized as a less invasive treatment[9,10,12–14,20].

Previous reports, based on the treatment of tibial nonunions, have shown a union rate ranging from 82 to 90%[9,12,20]. However, few clinical data are available regarding the effectiveness of bone marrow injection for femoral nonunions. In the present study, 4 long-standing nonunions of the femur completely united and one partially united leaving a 1×1 cm defect. The time-course in clinical and radiographic findings changed dramatically after bone marrow injection, suggesting a stimulatory effect of the procedure on the healing process at the nonunion site. Furthermore the effect of bone marrow injection was apparent even though the patients' activities were not restricted after the procedure.

Deficient bone healing in femoral shaft fractures usually arises from uncontrolled repetitive stresses, an insufficient blood supply at the fracture site, or infection[5]. Uncontrolled repetitive stresses attributable to inadequate fracture stabilization were thought to be the primary cause of the uninfected nonunions in this series. Femoral nonunions have been considered to invariably require surgical intervention to achieve union[5]. However, the present study shows that uninfected hypertrophic femoral nonunions which have been fixed by intramedullary nails can be treated by percutaneous bone marrow injection alone, even if stabilization by intramedullary nails itself has not been sufficient enough to achieve consolidation.

Two infected nonunions failed to heal. The indication of autologous bone marrow injection for

infected nonunions seems to be controversial. CONNOLLY et al[9] reported that 8 of 10 infected tibial nonunions healed with bone marrow injection combined with adequate fracture immobilization. SIM et al[20] obtained union in one of 2 infected nonunions of the tibia. The results suggest that infected nonunions are not always contraindication for this method of treatment. However, 2 out of the 4 failed cases in these two studies had infections. Moreover, CONNOLLY[9] states that 5 of the 10 infected fractures which underwent bone marrow injection had recurrent problems of infection and that subsequent treatments including drainage and sequestrectomy were required. Therefore, caution is recommended for bone marrow injection for infected nonunions. In femoral nonunions, adequate immobilization is unlikely to be achieved in contrast to tibial nonunions, unless internal fixation is performed. Thus, infected femoral nonunions, particularly with apparent loss of fixation, should be regarded as contraindication for the bone marrow injection. However, based on this result and our experience with tibial nonunions, previously infected nonunions respond to bone marrow injection. This technique can be effective for previously infected hypervascular nonunions if the infection has clinically and hematologically subsided.

Whether avascular nonunions are indicated or contraindicated for bone marrow injection could not be determined. It is demonstrated that an investigation of the relationship between histological and radiological features of human nonunions revealed some atrophic nonunions were cellular with evidence of active bone formation and were fairly well vascularized[1]. The response of avascular nonunions to bone marrow grafting must be further investigated.

Based on the results, uninfected hypervascular nonunion of the femur which has had intramedullarly nailing is an appropriate indication for percutaneous autologous bone marrow injection.

It is not known how the nonunion site should be prepared to efficiently stimulate healing. CONNOLLY et al[9,10] recommend insertion of the injection needle into the well-vascularized region of muscle attachment such as the posterolateral aspect of the tibia. However, no reports have made a precise description regarding this issue. We curette scar tissues and score the bone surface at the nonunion site at the time of bone marrow transplantation. In the case of fresh fracture, the sequence of events of healing begins immediately following injury, when growth factors, including transforming growth factor-β1 (TGF-β1) and platelet derived growth factor (PDGF), are released into the fracture hematoma by platelets, macrophages and other inflammatory cells[4]. These growth promoting substances are believed to play an important role in fracture healing[11,16]. Although the healing mechanism of nonunion after bone marrow transplantation has not been fully elucidated, we hypothesize that our maneuver may facilitate healing by creating a minor bone injury to initiate the process of repair in conjunction with bone marrow transplantation.

We injected marrow in volumes of 150 ml because previous reports stated that the optimal amount of injected marrow varied from 50 to 150 ml for nonunions in the lower extremity. However, the number of nucleated type cells in the aspirated marrow specimens were much lower than the normal value ($10–25 \times 10^4/mm^3$). This is probably because even careful needle sticks can draw off venous blood which result in dilution. It is reported that cell concentration of the transplanted bone marrow relates to osteogenic stimulation and centrifugated bone marrow enhances osteogenesis[8].

In conclusion, percutaneous autologous bone marrow injection into femoral nonunions is recommended as a minimally invasive method of treatment for uninfected hypervascular nonunions following intramedullary nail fixation. However, infected nonunions of the femur should be considered as contraindication for this technique.

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和文抄録

経皮的自家骨髄注入による大腿骨偽関節の治療

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7例の大腿骨偽関節症例に対して経皮的自家骨髄移植を施行した．Weber の分類法で，7例中6例は hypervascular nonunion，1例は avascular nonunion であった．2例は感染を合併しており，他の2例は感染の既往があった．方法として，経皮的に偽関節部の一部を掻爬し，腸骨から吸引した骨髄 150 ml を直ちに注入した．

1例には2回の自家骨髄注入を行った．髄内釘手術後の，感染を合併していなかった4例に9ヵ月以内に骨癒合が得られたが，感染のあった2例では癒合が得られなかった．この結果から，髄内釘施行後の感染の徴候を示さない大腿骨偽関節例に対して，経皮的自家骨髄移植は，より侵襲の少ない有用な治療方法と考えられた．